New Aspects of the Indium Chemistry of Carbonyl-β-lactams

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Abstract: Reactions of racemic as well as optically pure carbonyl-β-lactams with stabilized organo-indium reagents were investigated in aqueous media. The regio- and stereochemistry of the processes were generally good, offering a convenient asymmetric entry to densely functionalized hydroxy-β-lactams.

Key words: addition reactions, asymmetric synthesis, lactams, indium, organometallic reagents

The metallic element indium has a number of useful properties that suggest it should be useful in organic synthesis. It is unreactive towards air and water, is non-toxic, and is readily available in high purity due to the ease with which it zone refines. However, it is relatively rare, being the 63rd most abundant element in the Earth's crust, and hence available at prices similar to other rare elements such as silver. Generally speaking, indium exhibits a low heterophilicity in organic reactions and thus, oxygen- and nitrogen-containing functional groups are usually tolerated by organoindium reagents. Moreover, indium-assisted reactions display a low nucleophilicity thus permiting chemoselective transformations of groups of similar reactivity.[1] Despite its desirable chemical properties, indium has only recently been exploited in organic synthesis,[2] most notably in the generation of synthetically useful allylindium species.[3]

The development of new approaches to the stereocontrolled synthesis of β-lactam systems is a subject of great interest in the context of their possible use as biologically active compounds[4] or as versatile chiral building blocks.[5] On the other hand, the chiral β-amino alcohol moiety is present in many biologically important molecules such as dipeptide isosteres, statine and its analogues, and therefore its stereocontrolled synthesis remains an intensive research area.[6]

On the other hand, the development of new carbon–carbon bond forming reactions is of particular interest in organic synthesis. Among the most fundamental and important reactions for constructing carbon–carbon bonds are the allylation, the propargylation–allenylation and the 1,3-butadien-2-ylation of aldehydes and ketones (carbonyls) with organometallic reagents. Although many efforts have been made in these fields with various types of carbonylic compounds, at the outset of the present studies little was known about the reactions of carbonyl-β-lactams with stabilized organometallic reagents. Thus, the information available on the use of β-lactams as chiral building blocks on the propargylation–allenylation reactions was very scarce; only Cho has recently reported the propargylmetalation of 6-oxopenicillanates in anhydrous and aqueous tetrahydrofuran.[7] Bose[8] and Paquette[9] have independently reported the allylindation of azetidine-2,3-diones. However, the asymmetric version was achieved with poor diastereoselectivity on azetidine-2,3-diones bearing a chiral auxiliary at nitrogen.[9]

Removing organic solvents in chemical synthesis is important in the drive towards benign chemical technologies. Recently, organometallic reactions in aqueous media have elicited considerable interest due to their synthetic advantages as well as its potential as an environmentally benign chemical process.[10] Since indium in aqueous solution has shown considerable promise in the addition of unsaturated halides to the carbonyl group, we decide to explore further the indium-mediated reactions of carbonyl-β-lactams with stabilized organic halides under Barbier-type conditions in aqueous media.

The carbon–carbon bond formation reactions were initially investigated through the indium-mediated allylations between the azetidine-2,3-diones **1** and allyl bromides in aqueous tetrahydrofuran at room temperature. In the event, the indium as mediator showed total diastereoselectivity and good yields (70–100%) on product formation during allylation reactions of azetidine-2,3-diones **1** with allyl bromide, 2-(bromomethyl)acrylic acid, and prenyl bromide, in an aqueous environmment (Table 1).[11] Since the main drawbacks of the Barbier-type carbon–carbon bond formation are long reaction times, we thought that the allylation reaction could proceed with rate enhancement in the presence of some additives. Indeed, the addition of ammonium chloride, indium trichloride or hafnium chloride to the aqueous medium shortened reactions times, exhibiting the same facial preference (see Table 1). It is to be presumed that the ionic strength enhancement of the reaction solvent provided by the ammonium chloride accelerated the process. Although the role of the indium- and hafnium-derived additives is not completely understood, it may be explained in terms of Lewis acid, which activates the carbonyl group and the softness of these organoindium reagents.

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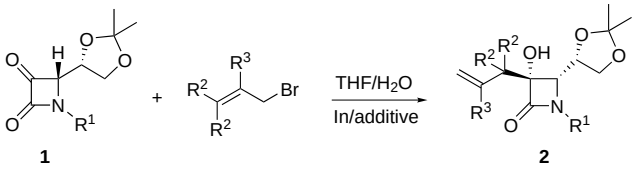
Table 1 Indium-Mediated Stereoselective Allylation of Enantiopure Azetidine-2,3-diones **1** in Aqueous Media[a]



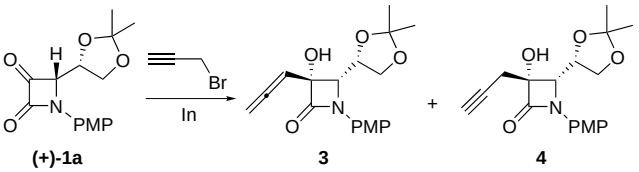
1 **2**

Product	R^1	R^2	R^3	Additive	T (°C)/t (h)	Yield (%)[b]
(+)-**2a**	PMP	H	H		20/18	73
(+)-**2a**	PMP	H	H	NH_4Cl	0/3	73
(+)-**2a**	PMP	H	H	$InCl_3$	20/2	73
(+)-**2a**	PMP	H	H	$HfCl_4$	20/1.5	73
(+)-**2d**	PMP	H	COOH	NH_4Cl	0/1.5	83
(–)-**2b**	2-Propenyl	H	H		20/18	70
(–)-**2f**	2-Propenyl	Me	H	NH_4Cl	0/1	80
(–)-**2g**	3-Butenyl	H	H	NH_4Cl	0/1	100
(–)-**2h**	2-Propynyl	H	CO_2H	NH_4Cl	0/1.5	99
(–)-**2h**	2-Propynyl	H	CO_2H	NH_4Cl	0/1.5	99

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. Only one isomer was detected in the ^1H NMR spectra of the crude reaction mixtures before purification.
[b] Yield of pure, isolated product with correct analytical and spectral data.

Once we had established the best reaction conditions to carry out the allylation reaction, our aim was to evaluate the feasibility of other related indium-mediated Barbier-type reactions in enantiomerically pure azetidine-2,3-diones, studying the diastereochemistry (*syn* vs. *anti*) and the regiochemistry of the connection (e.g., allenylation vs. propargylation). The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics. This metallotropic rearrangement often results in poor regioselection in the final organic product, because both organometallic species can react with the carbonyl compounds. The aim of achieving full control of regiochemistry prompted us to seek an aqueous indium-induced propargylation–allenylation reaction. For this purpose, azetidine-2,3-diones were treated with prop-2-ynyl bromides, bearing substituents of varying steric demand at C3. Not unexpectedly, the diastereoselectivity was complete in all cases. However, while the chemical yield of the addition was generally good, the regioselectivity of the process was a function of the nature of the propargyl bromide and in some cases of the system-solvent as well.

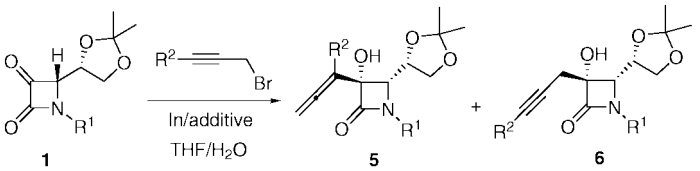
The regio- and diastereoselectivity of the addition reaction was initially investigated through the indium-mediated reaction between the azetidine-2,3-dione (+)-**1a** and propargyl bromide in aqueous tetrahydrofuran at room temperature. In the event, the 3-substituted 3-hydroxy-β-lactam moiety was obtained; however the observed regioselectivity was very poor (58:42) in favor of the allenic product. Surprisingly, the regiochemical preference was reversed on the indium-promoted reaction just by changing the solvent system (a saturated aqueous solution of NH_4Cl in THF was used instead of aqueous THF), with the expected alcohols **3** and **4** being obtained as a mixture of regioisomers in a ratio of **3**:**4**, 29:71 (Scheme 1).[12]



Scheme 1 Indium-mediated propargylation of azetidine-2,3-dione (+)-**1a** in aqueous media

Our next aim was to find a carbonyl propargylation–allenylation method that proceeds in a highly regioselective fashion by the use of 3-substituted prop-2-ynyl bromides through choice of reaction conditions. Metal-promoted reactions of azetidine-2,3-diones **1** with propargyl bromides bearing aliphatic or aromatic substituents at the terminal position, afforded the α-allenic alcohols **5** as essentially regio- and diastereoisomerically pure products. This observation is in sharp contrast to the metal-mediated reaction of propargyl bromide itself. The results are summarized in Table 2.

Table 2 Indium-Mediated Regio- and Stereoselective Allenylation of Azetidine-2,3-diones **1** in Aqueous Media[a]



1 **5** **6**

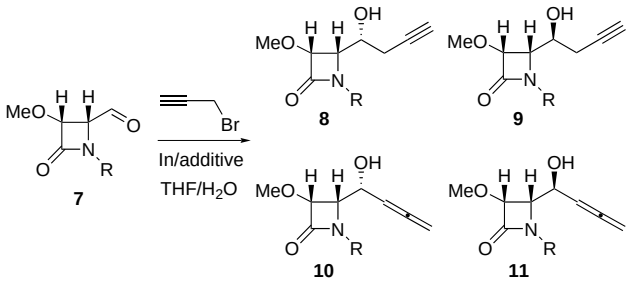
Compound	R^1	R^2	Additive	**5**:**6** ratio[b]	Yield (%)[c]
5a/**6a**	PMP	Me	NH_4Cl	100:0	74
5b/**6b**	2-Propenyl	Me	NH_4Cl	100:0	63
5c/**6c**	PMP	Ph	NH_4Cl	100:0	76
5c/**6c**	PMP	Ph		100:0	75
5d/**6d**	2-Propenyl	Ph	NH_4Cl	100:0	62
5e/**6e**	2-Propynyl	Ph	NH_4Cl	100:0	48

[a] All reactions were carried out on 1 mmol scale.
[b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification.
[c] Yield of pure, isolated product with correct analytical and spectral data.

We were interested in studying these addition reactions on other relevant class of non-racemic β-lactam carbonyl compounds. Thus, we evaluated the feasibility of the metal-mediated Barbier-type carbonyl propargylation–allenylation reactions of 4-oxoazetidine-2-carbaldehydes in eco-friendly media, studying the diastereochemistry (*syn* vs. *anti*) and the regiochemistry of the connection (e.g., allenylation vs. propargylation). Results from the metal-promoted reactions between aldehydes **7** and propargyl bromide are summarized in Table 3. The indium-promoted reaction proceeded with total diastereocontrol, but poor regiocontrol.[13] Unfortunately, the isomeric alcohols **8** and **10** could not easily be separated by gravity flow chromatography.

Next, we needed to find a carbonyl allenylation method that proceeds in a highly regio- and diastereoselective fashion. Thus, we used propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position. Indium-mediated reactions of aldehydes **7** with 3-substituted prop-2-ynyl bromides afforded the corresponding α-allenic alcohols **14** as regioisomerically pure products in diastereomeric ratios of about 90:10–100:0 (Table 4). The diastereomeric *syn*- and *anti*-alcohols were amenable to separation by bench chromatography.

Table 3 Indium-Mediated Propargylation of 4-Oxoazetidine-2-carbaldehydes **7** in Aqueous Media[a]

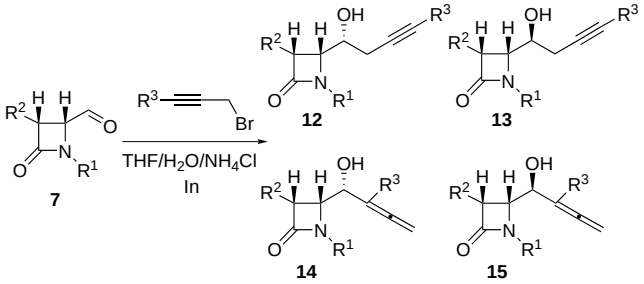


7 **8** **9** **10** **11**

Aldehyde	R	Additive	**8**:**9**:**10**:**11** Ratio[b]	Yield **8**/**10** (%)[c]
(+)-**1a**	2-Propenyl	NH_4Cl	55:0:45:0	72 (**8a**/**10a**)
(+)-**1f**	2-Propynyl	NH_4Cl	57:0:43:0	65 (**8b**/**10b**)
(+)-**1h**	4-Pentynyl	NH_4Cl	55:0:45:0	66 (**8c**/**10c**)
(+)-**1i**	PMP	NH_4Cl	80:0:20:0	74 (**8d**/**10d**)
(+)-**1i**	PMP		65:0:35:0	69 (**8d**/**10d**)

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$.
[b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification.
[c] Yield of pure, isolated product with correct analytical and spectral data.

Table 4 Indium-Mediated Regio- and Stereoselective Allenylation of 4-Oxoazetidine-2-carbaldehydes **7** in Aqueous Media[a]

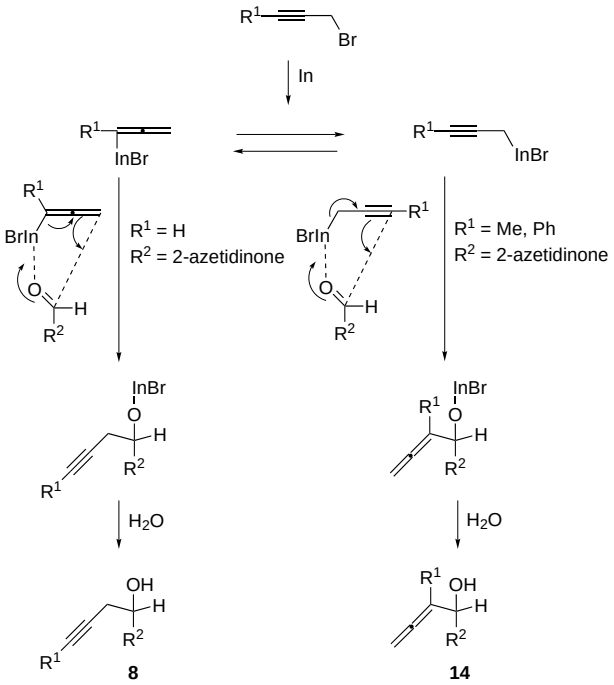


Aldehyde	R^1	R^2	R^3	**12**:**13**:**14**:**15** ratio[b]	Yield (%)[c]
(+)-**1a**	2-Propenyl	MeO	Me	0:0:95:5	75 (**14a**)
(+)-**1b**	3-Butenyl	MeO	Me	0:0:97:3	77 (**14b**)
(+)-**1c**	3-Butenyl	PhO	Me	0:0:90:10	92 (**14c**)
(+)-**1d**	PMP	2-Propenyloxy	Me	0:0:90:10	80 (**14d**)
(±)-**1e**	PMP	2-Propenyl	Me	0:0:90:10	90 (**14e**)
(+)-**1f**	2-Propynyl	MeO	Me	0:0:98:2	75 (**14f**)
(+)-**1g**	3-Butynyl	MeO	Me	0:0:93:7	69 (**14g**)
(+)-**1i**	PMP	MeO	Me	0:0:91:9	77 (**14h**)
(±)-**1j**	PMP	Ethenyl	Me	0:0:90:10	60 (**14i**)
(±)-**1k**	PMP	2-Propynyl	Me	0:0:90:10	90 (**14j**)
(+)-**1a**	2-Propenyl	MeO	Ph	0:0:100:0	64 (**14k**)
(+)-**1f**	2-Propynyl	MeO	Ph	0:0:95:5	60 (**14l**)
(+)-**1i**	PMP	MeO	Ph	0:0:90:10	84 (**14m**)
(±)-**1j**	PMP	Ethenyl	Ph	0:0:90:10	89 (**14n**)

[a] All reactions were carried out on 1 mmol scale.
[b] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification.
[c] Yield of pure, isolated product with correct analytical and spectral data.

It may be inferred that different steric effects in the organo-indium reagents derived from differently substituted propargyl bromides may be responsible for the different regiochemical preference of the propargyl–allenyl metals involved in the reaction, stabilizing one of the intermediates of the metallotropic equilibrium rather than the other. Probably, the isomerization of propargylindium to allenylindium is restricted by the steric effect of a substituent (R^1 = Me or Ph) in the bromopropyne (Scheme 2).

In contrast to the allylation and propargylation–allenylation, the analogous reaction involving butadienyl-metals has been much less investigated. Therefore, we were interested in exploring the indium-mediated 1,3-butadien-2-ylation of enantiomerically pure azetidine-2,3-diones in aqueous media using 1,4-dibromo-2-butyne **16** or 1,4-bis(methanesulfonyl)-2-butyne **17**. The indium-mediated reaction between the azetidine-2,3-dione (+)-**1a** and 1,4-dibromo-2-butyne in aqueous tetrahydrofuran (1:1) at room temperature afforded the 3-(1,3-butadien-2-yl)-3-hydroxy-β-lactam (+)-**18a** in 54% yield as the only regio- and stereoisomer (Table 5).[14] Because water is an economical solvent, we decide to increase the amount of water in the Barbier-type reaction. However, when the reaction was conducted in a THF–H_2O (1:5) mixture the coupling was not as efficient as before (18% yield). A higher proportion of THF beyond the 1:1 ratio in the solvent did not seem to improve the yield further. In addition, the ionic strength enhancement of the reaction solvent provided by the ammonium chloride was counter-productive for the indium-mediated 1,3-butadien-2-ylation. Thus, moving from THF–H_2O (1:1) to THF–NH_4Cl (aq sat.) (1:1) decreased the yield for the indium-promoted reaction between 1,4-dibromo-2-butyne and azetidine-2,3-dione (+)-**1a** (Table 5). The reaction time was increased 20 fold as the solvent changed from THF–H_2O (1:1) to a MeOH–H_2O (1:1) mixed solvent. No reaction was observed in THF–$NaHCO_3$ (aq sat.) (1:1). Next, we explored 1,4-bis(methanesulfonyl)-2-butyne **17** as a Barbier-type 1,3-butadien-2-ylating reagent, rather than 1,4-dibromo-

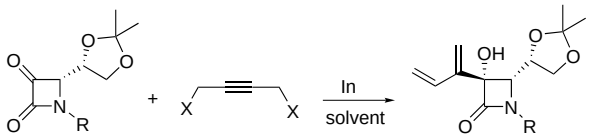


Scheme 2 Explanation for the regioselectivity in the propargylation–allenylation reaction of carbonyl-β-lactams

2-butyne **16**, because the mesylates are superior to the halides for ease of preparation and the stability of propargylic substrates. The bismesylate **17** was then reacted with azetidine-2,3-diones **1**, sodium iodide and indium in different aqueous media to afford the corresponding (buta-1,3-dien-2-yl)methanol derivatives **18** in moderate yield (up to 42%). In all cases, the same regioselectively was observed, but the conversion was enhanced as the solvent system changed from THF–H_2O (1:1) to THF–NH_4Cl (aq sat.) (1:5). These results suggest that the metal-promoted carbonyl 1,3-butadien-2-ylation in aqueous media may be quite sensitive to various factors.

From a mechanistic point of view, our results for the indium-mediated 1,3-butadien-2-ylation process of azetidine-2,3-diones using 1,4-bis(methanesulfonyl)-2-butyne or 1,4-dibromo-2-butyne could be explained as illustrated in Scheme 3.[15] It may be reasonable to postulate a metallotropic rearrangement between the propargylindium and allenylindium species. Their reactions with electrophiles suffer from competing reactions. Thus, both intermediates from this equilibrium are able to react with the azetidine-2,3-diones **1**, leading to the (buta-1,3-dien-2-yl)methanols **18** or homoallenic alcohols **19**. The formation of alcohols **18** and **19** is consistent with participation of the six-membered, cyclic transition structures **20** and **21**, respectively.

Table 5 Indium-Mediated Regio- and Stereoselective 1,3-Butadien-2-ylation of Azetidine-2,3-diones **1** in Aqueous Media[a]

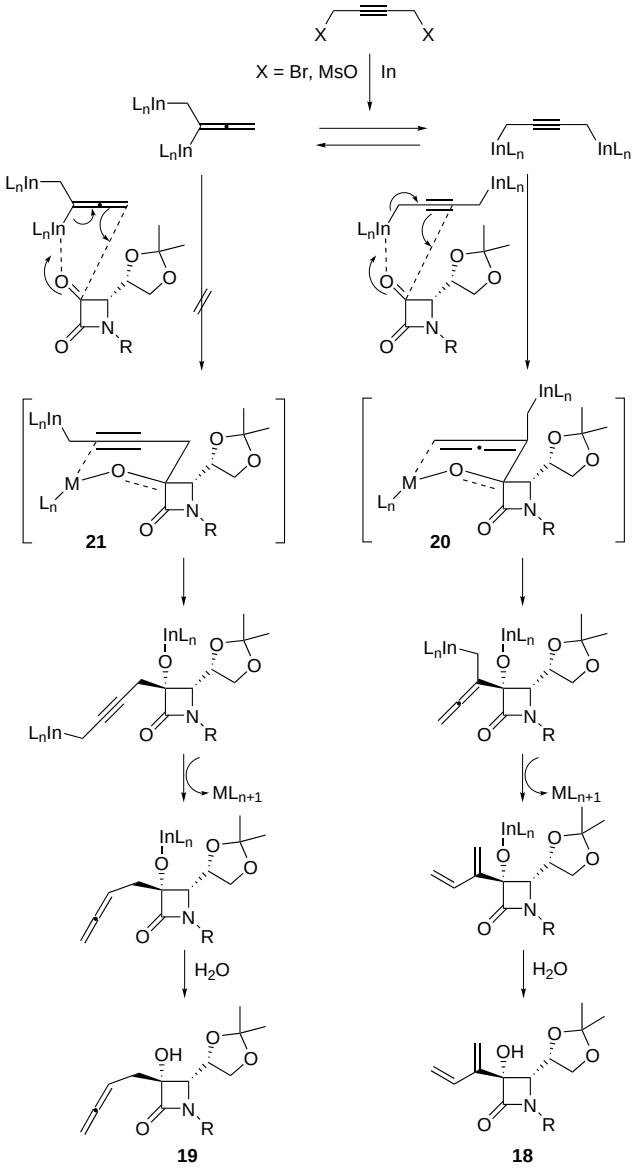


1 **16** X = Br, **17** X = MsO **18**

Compd[b]	R	X	System solvent	*t* (h)	Yield (%)[c]
(+)-**18a**	PMP	Br	THF–H_2O (1:1)	1	54
(+)-**18a**	PMP	Br	THF–H_2O (1:5)	1	18
(+)-**18a**	PMP	Br	THF–NH_4Cl (aq sat.) (1:1)	4	19
(+)-**18a**	PMP	Br	MeOH–H_2O (1:1)	20	26
(+)-**18a**	PMP	Br	THF–$NaHCO_3$ (aq sat.) (1:1)		
(+)-**18a**	PMP	MsO	THF–NH_4Cl (aq sat.) (1:5)	4	42
(+)-**18a**	PMP	MsO	THF–H_2O (1:1)	5	32
(–)-**18b**	2-Propenyl	Br	THF–H_2O (1:1)	1	62
(+)-**18c**	2-Propynyl	Br	THF–H_2O (1:1)	1	38
(+)-**18d**	3-Butenyl	Br	THF–H_2O (1:1)	1	45
(–)-**18b**	2-Propenyl	MsO	THF–NH_4Cl (aq sat.) (1:5)	4	33
(+)-**18c**	2-Propynyl	MsO	THF–NH_4Cl (aq sat.) (1:5)	4	37
(+)-**18d**	3-Butenyl	MsO	THF–NH_4Cl (aq sat.) (1:5)	4	34

[a] All reactions were carried out on 1 mmol scale.
[b] Obtained as single regio- and stereoisomers, to judge by the ^1H NMR spectra of the crude reaction mixtures before purification.
[c] Yield of pure, isolated product with correct analytical and spectral data.

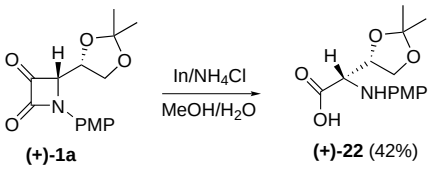
It seems reasonable to propose that the regiochemical preference observed on the indium-promoted reactions of 1,4-dibromo-2-butyne and 1,4-bis(methanesulfonyl)-2-butyne with azetidine-2,3-diones must be controlled by steric effects. Probably, the isomerization of propargylmetal to allenylmetal is prohibited by the steric effect of both ML_n substituents. Thus, the propargylindium reagent undergoes nucleophilic addition to produce exclusively allenyl compounds, which after protiodemetalation gave 1,3-butadien-2-yl alcohols **18** (Scheme 3).



Scheme 3 Mechanistic explanation for the regioselective formation of alcohols **18**

The stereochemistry at the C3-heterosubstituted quaternary center for compounds **2**, **4**, **5** and **18** was assigned by qualitative homonuclear NOE difference spectra. The stereoselectivity in the addition reaction of these stabilized organo-indium reagents with azetidine-2,3-diones **1** is believed to be controlled by the bulky acetonide at C-4, in which one face of the carbonyl group is blocked preferentially, thus the organoindium species being delivered to the less hindered face. Derivatization of the alcohols **8** and **14** with (*R*)- and (*S*)-acetylmandelic acids allowed assignment of the configuration at the carbinolic stereocenter. The stereochemical result can be interpreted by the Felkin–Anh model.

As well as the above addition reactions, indium itself was able to promote the reaction of azetidine-2,3-dione (+)-**1a** and water, with concomitant CO extrusion. In this way, a one-step synthesis of the α-amino acid (+)-**22** was achieved (Scheme 4).



(+)-1a **(+)-22** (42%)

Scheme 4 Indium-mediated synthesis of α-amino acid (+)-**22** from α-keto lactam (+)-**1a**

In conclusion, we have developed a very efficient asymmetric synthesis of highly substituted monocyclic β-lactams and α-amino acids using indium chemistry in aqueous media. Furthermore, additional transformations of the alkene, alkyne, and allene moieties can be envisioned thus providing an array of useful building blocks.

All commercially available compounds were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, δ = 0.0), or $CDCl_3$ (^{13}C, δ = 76.9). Low and high-resolution mass spectra were taken on a HP5989A spectrometer using the chemical ionization modes (CI) unless otherwise stated. Electrospray ionization (ESI) was performed on a Bruker ESQUIRE LC at 400 eV. Specific rotation $[\alpha]_D$ is given in deg per dm at 20 °C, and the concentration (*c*) is expressed in g per 100 mL.

Indium Promoted Reaction Between Allyl Bromides and Azetidine-2,3-diones 1 in an Aqueous Medium Containing NH_4Cl; General Procedure for the Synthesis of Homoallylic Alcohols 2

The appropriate allyl bromide (363 mg, 3.0 mmol) was added to a well-stirred suspension of the corresponding α-keto lactam (1.0 mmol) and indium powder (688 mg, 6.0 mmol) in THF–NH_4Cl (aq sat.) (1:5, 5 mL) at 0 °C. After disappearance of the starting material (TLC) the mixture was extracted with EtOAc (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (EtOAc–hexanes mixtures) gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **2** follow.

(3*R*,4*S*)-3-(2-Carboxy-2-propenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone [(+)-2d]

From azetidine-2,3-dione (+)-**1a** (53 mg, 0.18 mmol), compound (+)-**2d** was obtained.

Yield: 58 mg (83%); colorless oil; $[\alpha]_D$ +47.4 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3205, 1708 cm^{-1}.

^{1}H NMR: δ = 1.28 and 1.47 (s, 3 H each), 2.86 (m, 2 H), 3.65 (m, 1 H), 3.76 (s, 3 H), 3.99 (m, 1 H), 4.27 (m, 2 H), 5.69 (s, 1 H), 6.35 (s, 1 H), 6.81 (d, 2 H, *J* = 8.0 Hz), 7.61 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR: δ = 171.0, 168.6, 156.7, 130.7, 128.2, 120.1, 119.9, 113.9, 109.4, 83.5, 77.2, 68.8, 66.5, 55.4, 38.3, 26.6, 24.9.

MS (CI): *m*/*z* = 334 (M^+ +1, 100), 333 (M^+, 25).

Anal. Calcd for $C_{19}H_{22}NO_7$: C, 60.63; H, 5.84; N, 3.72. Found: C, 60.70; H, 5.81; N, 3.70.

(3*R*,4*S*)-3-(1-Methyl-2-propenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(2-propenyl)-2-azetidinone [(–)-2f]
From α-keto lactam (–)-**1b** (52 mg, 0.23 mmol), compound (–)-**2f** was obtained.

Yield: 54.2 mg (80%); colorless oil; $[\alpha]_D$ –35.9 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$): 3332, 1744 cm^{-1}.

^{1}H NMR: δ = 1.13 (s, 6 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 3.49 (d, 1 H, *J* = 6.8 Hz), 3.65 (dd, 1 H, *J* = 15.1, 8.3 Hz), 3.71 (dd, 1 H, *J* = 8.8, 5.9 Hz), 4.01 (br s, 1 H), 4.12 (dd, 1 H, *J* = 8.8, 6.8 Hz), 4.21 (dd, 1 H, *J* = 14.6, 4.9 Hz), 4.29 (q, 1 H, *J* = 6.3 Hz), 5.20 (m, 4 H), 5.72 (m, 1 H).

^{13}C NMR: δ = 169.7, 142.6, 131.5, 119.2, 114.7, 109.6, 88.9, 76.4, 66.7, 61.5, 43.5, 41.1, 26.6, 25.1, 21.6, 21.2.

MS (CI): *m*/*z* = 296 (M^+ + 1, 100), 295 (M^+, 24).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.14; H, 8.56; N, 4.70.

Indium Promoted Reaction Between 3-Substituted 1-Bromo-2-propynes and Carbonyl-β-lactams 1 or 7 in an Aqueous Medium Containing NH_4Cl; General Procedure for the Synthesis of α-Allenic Alcohols 5 and 14
The appropriate 1-bromo-3-substituted-2-propyne (3.0 mmol) was added to a well stirred suspension of the corresponding carbonyl-β-lactam (1.0 mmol) and indium powder (6.0 mmol) in THF–NH_4Cl (aq sat.) (1:5, 5 mL) at 0 °C. After disappearance of the starting material (TLC) the mixture was extracted with EtOAc (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (EtOAc–hexanes mixtures) gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **5** and **14** follow.

(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-3-(1-methyl-1,2-propadienyl)-2-azetidinone [(+)-5a]
From azetidine-2,3-dione (+)-**1a** (50.5 mg, 0.173 mmol), compound (+)-**5a** was obtained.

Yield: 44 mg (74%); colorless oil; $[\alpha]_D$ +75.4 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 3340, 2991, 1940, 1742 cm^{-1}.

^{1}H NMR: δ = 1.36 (s, 3 H), 1.51 (s, 3 H), 1.85 (t, 3 H, *J* = 3.0 Hz), 3.79 (s, 3 H), 3.80 (dd, 1 H, *J* = 8.8, 6.4 Hz), 4.14 (br s, 1 H), 4.24 (d, 1 H, *J* = 7.7 Hz), 4.32 (dd, 1 H, *J* = 8.8, 6.8 Hz), 4.49 (q, 1 H, *J* = 7.0 Hz), 4.98 (dd, 2 H, *J* = 6.4, 3.0 Hz), 6.86 (dd, 2 H, *J* = 7.0, 2.5 Hz),

7.63 (dd, 2 H, *J* = 7.0, 2.5 Hz).

^{13}C NMR: δ = 205.2, 166.6, 156.7, 130.7, 120.0, 114.0, 109.7, 98.6, 83.5, 79.4, 76.8, 66.8, 66.5, 55.4, 26.6, 25.0, 13.9.

MS (CI): *m*/*z* = 346 (M^+ + 1, 100), 345 (M^+, 20).

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.13; H, 6.65; N, 4.00.

(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-3-(1-phenyl-1,2-propadienyl)-1-(2-propenyl)-2-azetidinone [(–)-5d]
From azetidine-2,3-dione (–)-**1b** (58 mg, 0.257 mmol), compound (–)-**5d** was obtained.

Yield: 54 mg (62%); colorless oil; $[\alpha]_D$ –75.8 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 3334, 2991, 1940, 1745 cm^{-1}.

^{1}H NMR: δ = 1.34 (s, 3 H), 1.40 (s, 3 H), 3.67 (dd, 1 H, *J* = 8.8, 5.4 Hz), 3.68 (m, 1 H), 3.80 (d, 1 H, *J* = 7.1 Hz), 4.17 (dd, 1 H, *J* = 8.8, 6.8 Hz), 4.22 (ddt, 1 H, *J* = 15.4, 4.6, 1.7 Hz), 4.44 (dd, 1 H, *J* = 7.1, 5.6 Hz), 4.47 (s, 1 H), 5.13 (m, 2 H), 5.21 (s, 2 H), 5.61 (m, 1 H), 7.28 (m, 3 H), 7.59 (m, 2 H).

^{13}C NMR: δ = 207.3, 168.8, 132.8, 131.3, 128.5, 127.6, 118.3, 109.7, 105.8, 84.8, 80.3, 76.0, 66.6, 64.9, 43.4, 26.5, 25.0.

MS (CI): *m*/*z* = 342 (M^+ + 1, 100), 341 (M^+, 24).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.44; H, 6.82; N, 4.12.

(3*R*,4*S*)-1-(3-Butenyl)-4-[(*R*)-1-hydroxy-2-methyl-2,3-butadienyl]-3-methoxy-2-azetidinone [(+)-14b]
Aldehyde (+)-**1b** (95 mg, 0.52 mmol), after chromatography of the residue (hexanes–EtOAc, 1:1), gave compound (+)-**14b**.

Yield: 95 mg (77%); colorless oil; $[\alpha]_D$ +46.1 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 3421, 2992, 1942, 1747 cm^{-1}.

^{1}H NMR: δ = 5.73 (m, 1 H), 5.06 (m, 2 H), 4.81 (q, *J* = 3.0 Hz, 1 H), 4.42 (d, *J* = 4.8 Hz, 1 H), 4.23 (m, 1 H), 3.94 (t, *J* = 4.6 Hz, 1 H), 3.55 (s, 3 H), 3.50 (m, 1 H), 3.20 (ddd, *J* = 13.6, 7.0, 6.0 Hz, 1 H), 2.67 (br s, 1 H), 2.31 (m, 2 H), 1.79 (t, *J* = 3.0 Hz, 3 H).

^{13}C NMR: δ = 205.4, 167.7, 135.0, 116.8, 99.8, 83.3, 77.2, 70.3, 59.5, 59.3, 40.7, 31.9, 16.0.

MS (CI): *m*/*z* = (%): 238 (M^+ + 1, 100), 237 (M^+, 19).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.0; N, 5.90. Found: C, 65.87; H, 8.09; N, 5.88.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-phenyl-2,3-butadienyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone [(+)-14m]
Aldehyde (+)-**1i** (46 mg (0.197 mmol), after chromatography of the residue (CH_2Cl_2–EtOAc, 9.5:0.5), gave compound (+)-**14m**.

Yield: 58 mg (84%); colorless oil; $[\alpha]_D$ +99.8 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$): 3419, 2989, 1940, 1746 cm^{-1}.

^{1}H NMR: δ = 7.51 (m, 2 H), 7.32 (dd, *J* = 6.8, 2.2 Hz, 2 H), 6.87 (dd, *J* = 6.8, 2.2 Hz, 2 H), 7.31 (m, 3 H), 5.22 (m, 3 H), 4.72 (d, *J* = 4.9 Hz, 1 H), 4.48 (dd, *J* = 4.9, 2.7 Hz, 1 H), 3.79 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR: δ = 208.2, 164.4, 156.8, 133.9, 129.6, 128.6, 127.3, 126.8, 119.8, 114.5, 106.0, 84.3, 80.2, 67.1, 60.0, 59.4, 55.5.

MS (CI): *m*/*z* = (%): 352 (M^+ + 1, 100), 351 (M^+, 34).

Anal. Calcd for $C_{21}H_{21}NO_4$ (289.3): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.86; H, 6.00; N, 3.97.

Indium Promoted Reaction Between 1,4-Dibromo-2-butyne and Azetidine-2,3-diones in Aqueous Medium; General Procedure
1,4-Dibromo-2-butyne **16** (2.0 mmol) was added to a well stirred suspension of the corresponding α-keto lactam **1** (1.0 mmol) and indium powder (1.99 mmol) in THF–H_2O (1:1, 5 mL) at 0 °C. After 1 h at r.t., sat. aq NH_4Cl (2 mL) was added at 0 °C, and the mixture was allowed to warm to r.t., before being extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (EtOAc–hexane mixtures), gave analytically pure compounds **18**. Spectroscopic and analytical data for some representative forms of **18** follow.

(3*R*,4*S*)-3-(1,3-Butadien-2-yl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(2-propynyl)-2-azetidinone [(+)-18c]
From azetidine-2,3-dione (–)-**1c** (64 mg, 0.287 mmol), compound (+)-**18c** was obtained.

Yield: 30 mg (38%); colorless oil; $[\alpha]_D$ +1.7 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 3344, 1743 cm^{-1}.

^1H NMR: δ = 1.37 (s, 3 H), 1.48 (s, 3 H), 2.28 (t, 1 H, *J* = 2.6 Hz), 3.90 (m, 4 H), 4.20 (m, 1 H), 4.53 (m, 2 H), 5.22 (d, 1 H, *J* = 11.0 Hz), 5.37 (s, 1 H), 5.47 (s, 1 H), 5.56 (dd, 1 H, *J* = 17.6, 1.2 Hz), 6.30 (ddd, 1 H, *J* = 17.6, 11.0, 0.7 Hz).

MS (CI): *m*/*z* = 278 (M^+ + 1, 100), 277 (M^+, 14).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.91; H, 6.93; N, 5.04.

(3*R*,4*S*)-3-(1,3-Butadien-2-yl)-1-(3-butenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-azetidinone [(+)-18d]
From azetidine-2,3-dione (–)-**1d** (54 mg, 0.226 mmol), compound (+)-**18d** was obtained.

Yield: 22 mg (34%); colorless oil; $[\alpha]_D$ +1.1 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$): 3343, 1745 cm^{-1}.

^1H NMR: δ = 1.36 and 1.45 (s, each 3 H), 2.37 (m, 2 H), 3.27 (m, 1 H), 3.57 (d, 1 H, *J* = 7.3 Hz), 3.67 (m, 2 H), 4.22 (dd, 1 H, *J* = 8.7, 6.7 Hz), 4.18 (s, 1 H), 4.41 (dt, 1 H, *J* = 7.0, 5.8 Hz), 5.08 (m, 2 H), 5.19 (dd, 1 H, *J* = 11.0, 1.5 Hz), 5.33 (s, 1 H), 5.37 (s, 1 H), 5.54 (dd, 1 H, *J* = 17.6, 1.6 Hz), 5.77 (m, 1 H), 6.25 (ddd, 1 H, *J* = 17.3, 11.0, 0.9 Hz).

^{13}C NMR: δ = 169.1, 143.6, 134.8, 133.7, 117.3, 117.1, 114.8, 109.7, 85.8, 76.1, 66.6, 65.6, 40.4, 31.6, 26.6, 25.0.

MS (CI): *m*/*z* = 294 (M^+ + 1, 100), 293 (M^+, 19).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.59; H, 7.88; N, 4.75.

Indium Promoted Reaction Between Azetidine-2,3-dione (+)-1a and Water; Procedure for the α-Amino Acid (+)-22
A suspension of the azetidine-2,3-dione (+)-**1a** (0.5 mmol), indium powder (5 mmol), and solid NH_4Cl (3 mmol) in aq MeOH (10 mL; 5% of H_2O) was stirred at r.t. for 3 days. The solvent was removed under reduced pressure and, after flash chromatography (hexanes–EtOAc, 1:1), compound (+)-**22** was obtained in analytically pure form.

Yield: 42%.

(+)-(2*S*)-2-(4-Methoxyphenylamino)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetic Acid [(+)-22]
Colorless solid; mp 185–186 °C (hexanes–EtOAc); $[\alpha]_D$ +34.8 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3345, 3130, 1710 cm^{-1}.

^1H NMR: δ = 6.93 (br s, 1 H), 6.80 (d, *J* = 8.9 Hz, 2 H), 6.62 (d, *J* = 8.9 Hz, 2 H), 5.63 (br s, 1 H), 4.59 (m, 1 H), 4.11 (dd, *J* = 8.6, 6.6 Hz, 1 H), 3.97 (dd, *J* = 8.6, 5.6 Hz, 1 H), 3.76 (s, 3 H), 3.64 (d, *J* = 4.1 Hz, 1 H), 1.49 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR: δ = 174.2, 153.4, 140.9, 115.1, 109.9, 75.5, 66.8, 61.9, 55.8, 26.6, 24.8.

MS (CI): *m*/*z* = (%) 282 (M^+ + 1, 100), 281 (M^+, 14).

Anal. Calcd for $C_{14}H_{19}NO_5$ (281.3): C, 59.78; H, 6.81; N, 4.98. Found: C, 59.85; H, 6.79; N, 5.00.

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